V. REMARKS/ARGUMENTS

- *STATUS OF THE CLAIMS*

Claims 16, 18, 40, 41, 44-45, 47 were pending during the issuance of the Office Action. Claims 16, and 18 are cancelled herein. Claims 40, 41, 45 and 47 are amended herein. Claims 48 – 53 are added herein. The amendments to the claims are pro forma and it is asserted that they do not add new matter. Support for the new claims is found, among other places, at paragraphs [0032], [0194], and [0195]. It is asserted that the new claims also do not introduce new matter.

- *OBJECTIONS*
  - *OBJECTIONS TO CLAIMS AND SPECIFICATION*
    - *Examiner's Stance*

The Examiner has raised no objections.

    - *Applicants' Response*

N/A

- *REJECTIONS*
  - *REJECTION UNDER 35 U.S.C. §101*
    - *Examiner's Stance*

Examiner contends that claims 16, 18, 40,41, 45 & 47 are directed to non-statutory subject matter. Examiner alleges that the programmed steps described in these claims describe non-functional descriptive material, "as not requisite functionality is present to satisfy the practical application requirement." (page 2 – 3 of the Office Action). The

Examiner asserts that the claims are directed to "nonfunctional descriptive material," and relate to programs that are not statutory because "they are not capable of causing a functional change in the computer." The Examiner asserts the rejections could be overcome by amending the claims "to recite that a result of the method is 'displayed' or 'outputted'" or by amending the claims to "include a step of a physical transformation of matter (e.g. assay)."

- *Applicants' Response*

The Applicants respectfully traverse the Examiner's 35 U.S.C. §101, in part, arguing that the Examiner has misinterpreted the claims as being directed to software per se. Irrespective, Applicant notes that the rejection of claims 16, and 18 are hereby mooted by the cancellation of such claims herein. Further, as claims 40, 41, and 45 now depend from new claim 48, it is asserted that the 35 U.S.C. §101 rejection of such claims is mooted. New claim 48 clearly and amended claim 47 assert patentable subject matter.

- *REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH*

- *Examiner's Stance*

Examiner rejects Claims 16, 18, 40, 41, 45, and 47 under 35 U. S. C. 112 , first paragraph, alleging that the claims are not described in the specification in such away as to enable one skilled in the art without undue experimentation. The Examiner summarizes the eight Wands factors used to determine the need for "undue experimentation" to assert that the claims are not enabled. The Examiner asserts that as cell staining or cell tagging are reflected in the claims the inventive embodiments asserted therein are not enabled. The Examiner asserts that the practitioner would have to turn to "trial and error experimentation

to determine if the claimed method steps would yield a color image" and this represents undue experimentation.

- *Applicants' Response*

Applicants respectfully strongly disagree with the Examiner's assertion of lack of enablement with respect to unamended claims 16, 18, 40, 41, 45, and 47. The Examiner respectfully is attempting to import limitations of embodiments in the specification into the claims. Enablement is determined from the view of one of ordinary skill in the art reading the claims in light of the specification. Clearly the specification gives copious detail on how to transact the steps of the claims as drafted. Quite simply, the Examiner's assertions of lack of enablement under Section 112, first paragraph, are wholly without merit.

Concerning the Examiner's allegation that undue experimentation is required for measurement of "... pre-set criteria in terms of size, morphology, and characteristic cell markers ... [needed to] identify a rare cell..." Applicants respectfully disagree. The pre-set criteria is unique to the cell of interest. The preset criteria can represent a fetal cell in maternal blood as exemplified and described in detail as quoted by Examiner where the cell is fixed and stained to yield the characteristics color of fetal hemoglobin converted from RGB to HLS. Contrary to the Examiner's allegation, the staining and fixing is described **[0109-0113]** and represents highly robust methodology familiar to those skilled or those with only ordinary skill in the Art. This is the first signal and with the recorded coordinates the second signal can be automatically generated by the direct application of the reagent dispensed in an automated fashion. It is noted that as copiously described in the instant Specification

and known in the art, fetal cells are rare cells contrary to the Examiner's comment that "the instant claims are drawn to rare cells and not fetal cells." As also indicated in the Specification the first signal could be the mere presence of the cell, unique morphology (roundness, elongations, pseudopodia, etc.) as well as size in stained or unstained cells. Hematologists and pathologists readily and visually recognize changes in size and morphology of cells such as bidiscoidal (donut) shape verses a nucleated fetal cell or the presence of blast cells needed to differentiate leukemic patients from normal or to assess success of treatment. This applies to unstained cells as well as stained cells. Accordingly, it was not the intention of the Applicant to teach redundantly these well established methods of fixing, staining.

Concerning "characteristic markers", also alleged by the Examiner to require undue experimentation to enable, the Applicants thoroughly document many but not all markers in multiple parts of the specification. Furthermore, the Applicants point out that those in the art have a high level of skill and that the reagents for detections of said markers are readily available. For many of the cancer markers cited **[0079-0102],** these reagents are antibodies directed to the said matter or gene product. These antibodies such as those directed to BMP **[0084]** are commercially available as well as antibody conjugates to amplify their detection. Additionally, sequences of the markers listed are known permitting design and production of antibodies needed to facilitate the investigators' needs. It is respectfully asserted here that regarding the reagents, the level of skill of those in the art is sufficient to obtain and use these reagents to prepare samples necessary of automated analysis by the instant invention.

The "preset criteria" therefore comprises information derived from "size, morphology and characteristic markers" readily known to those skilled the Art.

The Examiner claims that there are "no cellular identification labels or stains that one of skill in the art would be able to generate an image for processing and identification of a rare cell." Applicants respectfully and emphatically traverse this rejection partly for reasons discussed above. Of the cancer biomarkers described on page **[0079-0102]** of the Specification, antibodies are commercially available; sequences are also available and public at NCBI. The availability of sequence enables the investigator if so inclined to order the preparation of specially designed antibodies. Many rare cancer cells such as blast cells are readily discernable visually by pathologists, hematologists and others skilled in the Art. Specifically, anti $Hb_{epsilon}$ (fetal hemoglobin) is a reagent exemplified **[0111]** for the identification of a fetal erythrocyte. Accordingly, the Applicant asserts that the labels in the form of the antibodies or visual inspection or stains are described sufficiently to enable.

The Examiner contends that with "absent steps of labeling or staining in the claims, one of skill in the art would not know how to generate or receive a color image signal." On the contrary since one of ordinary skill is familiar with conventional staining and fixing protocols necessary to "generate … a color image signal", Applicants deem these conventional staining techniques not core to claimed method of locating and identifying rare cell candidates. Receiving a color image signal is supported in detail within the specifications and described in detailed in figures (figure 3, Figures 4A and 4b steps 405, 407, 409,411, 413, 5 and in text **[0150-0161]**. Accordingly the applicants assert the claims enabling with respect to generating and receiving color images. Furthermore the skilled practitioner would not need to undertake undue experimentation.

Irrespective, the Examiner's 35 U.S.C. §112, First Paragraph, rejection with respect to claims 16, and 18 are mooted by cancellation of such claims. Such rejection with respect to claims 40, 41 and 45 are also mooted, as such claims now depend from new claim 48. Applicant asserts that amended claim 47 and new claim 48 clearly are enabled and would not require taking the teaching of the Specification undue experimentation.

- *REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH*
  - *Examiner's Stance*

Claims 16, 18, 40, 41, 45, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicant regards as the invention.

The Examiner asserts with respect to claim 47, from which all other claims previously depended:

> Claim 47 recites "starting a microscope objective from an origin...to locate and digitize". The Examiner urges that it is unclear how the step of starting a microscope includes locating and digitizing a native or stained color image". The Examiner opines that a step is missing and requests clarification.
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> Claim 47 recites "measuring pre-set criteria of the digitized image...in terms of size, morphology, and characteristic cell markers". The Examiner queries: "Does Applicant intend that the pre-set criteria are size, morphology, and characteristics cell markers?" The Examiner requests clearer language in the claim.
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> Claim 47 recites "measuring...while enhancing detection of". The Examiner states that it is unclear whether such steps occur

simultaneously, one after the other or in some other sequence. Clarification is requested.

Claim 47 recites "identifying said detected rare cell by using". The Examiner asserts that there is insufficient antecedent basis in the claim for "detected rare cell". The Examiner suggests that Applicant intends "said detected rare cell candidate" or "said detected rare cell image". Clarification is requested.

Claim 47 recites, "identifying said detected rare cell by using the automatically recorded coordinates of said rare cell to locate over said rare cell a computer-controlled reagent dispensing system programmed to apply selectively a specific tag or label to said rare cell in situ." The Examiner urges that is it is unclear what is intended by this step, in particular how ". identifying can locate a reagent dispensing system." The Examiner points to his enablement rejection and seeks clarification.

- *Applicants' Response*

Applicants respectfully traverse all of the Examiner's 35 U.S.C. §112, Second Paragraph rejections, asserting that one of ordinary skill in the art would understand such claims as particularly pointing out and distinctly claim patentable subject matter which are embodiments of the present invention.

Irrespective, Applicants note that the Examiner's 35 U.S.C. §112, Second Paragraph rejections are mooted with respect to claims 16, and18 as such claims are cancelled herein. Claim 47 as amended is now more definitely directed to a method embodiment described in the Specification, especially in paragraph [0195], the method being for rare cell light and fluorescence microscopic image detection and identification, comprising the automatic motorized steps of: (i) locating and digitizing

a bright field and fluorescence microscopic image of a rare cell candidate or a cell blob containing a rare cell candidate with a microscope objective and digitally record and store x and y coordinates as well as focal y-z coordinates thereof, starting from and relating to a position at a point of origin (x_1,y_1) of an optical field;

(ii) detecting by pre-set criteria according to cell size, cell morphology, and characteristic cell markers the digitized image of a rare cell or rare cell nucleus,

(iii) identifying said detected rare cell candidate image or a cell blob containing a rare cell candidate image by locating with a sensor a motorized and computer-controlled tagging or labeling reagent dispensing system over said rare cell image according to the x, y and y-z position coordinates to apply automatically and selectively one or more specific tag or label to said rare cell image *in situ* .

Furthermore, as claims 40, 41, and 45 have been amended to depend from new independent claim 48, Applicants assert once more that such rejection is mooted with respect to these claims. Applicant asserts that new claim 48 is written to more clearly set forth the embodiments presently being sought.

- *REJECTION UNDER 35 U.S.C. §102(E)*
  - *Examiner's Stance*

Claims 16, 18, 40, 41, 45, and 47 are rejected under 35 U.S.C. 112, as being anticipated by US 6,169,816 (Ravkin). The Examiner asserts that Ravkin teaches computer implemented imaging of a smear of fetal nucleated red blood cells and other objections, such as red blood cells and white blood cells. The Examiner states that the Ravkin reference teaches staining nuclei with a fluorescent dye and the use of a dye that selective stains fetal hemoglobin in the cytoplasm of fetal NRBCs, and then using the two different illumination

schemes to find candidate regions of interest for further processing. He further alleges that Ravkin teaches a set of features that identify fetal NRBCs from other types of cells using an antibody to produce a signal. He further contends that the Ravkin reference discloses "the invention is carried out to identify objects for further analysis such as FISH."

- *Applicants' Response*

Applicants respectfully disagree with, and traverse, the Examiner's 35 U.S.C. §102(e) rejections with respect to unamended claims 16, 19, 40, 41, 45 and 47 pending at the time of the Office Action. The Applicants assert that Ravkin fails to disclose each and every limitation of former independent claim 47, from which claims 16, 19, 40, 41, and 45 previously depended. The Applicants in particular traverse the Examiners' allegation on page 9 (line 18-19) of the Office action that "the preparation of the slides with reagent is automated" in the Ravkin reference as indicated by column 3, lines 1-10 & 25-57 of Ravkin. Applicants assume that the Examiner has misread this citation as there is no mention of automation. An explicit feature of the instant invention is the automated detection of rare cells. To this end, the Applicants disclose and claim the automated detection of rare cells. On the contrary, Ravkin fails to disclose or claim an automated method of rare cell identification comprising the steps of amended claim 47.

Irrespective, Applicants assert that the rejection of claims 16, and 18 are mooted as such claims have been cancelled herein. Furthermore, as claims 40, 41, and 45 now depend on new independent claim 48, such claims now import the limitations of such claim. Applicants assert that the Ravkin reference not even remotely discloses each of the elements of the method of amended claim 47 and new independent claim 48, in particular in conjunction with the use of a computerized microscope system that can locate a reagent

dispenser at the coordinates of a signal indicative of the presence of a labeled rare cell or blob comprising a labeled rare cell and to cause the same to dispense a volume of material.

CONCLUSION

Applicants assert that this response is a good faith effort to place the application in condition for allowance. Applicants respectfully seek early allowance of the pending claims.

Respectfully submitted,

Date: February 11, 2008

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